

04-C-0079: Pediatric Phase I Trial of BL22 for Refractory CD22-Positive Leukemias and Lymphomas

This is a phase I trial of the recombinant immunotoxin RFB4(dsFv)-PE38 (BL22) in pediatric patients with refractory CD22-positive lymphoid malignancies (ALL, NHL). Therapeutic efficacy was observed in a phase I trial of BL22 in adults with lymphoid malignancies that expressed high levels of the CD22 antigen on their surface. In vitro cytotoxicity was also demonstrated in the majority of pediatric B-precursor ALL samples. The immunotoxin BL22 will be administered to children and adolescents with CD22-positive hematopoietic malignancies that have been refractory to standard therapy. Clinical response will be evaluated using routine hematologic and clinical evaluation and, when appropriate, by monitoring the phenotype of circulating malignant cells, bone marrow, or tumor tissue. BL22 pharmacokinetics and levels of anti-immunotoxin antibodies will also be monitored. It is hoped that this phase I trial will lead to the development of a new, specific therapy for CD22-positive hematopoietic malignancies of childhood and adolescence.

ELIGIBILITY CRITERIA

Age: > 6 months and < 25 years.

Histologic diagnosis: All patients must have a histologically confirmed diagnosis of acute lymphoblastic leukemia (ALL) or non-Hodgkin's lymphoma (NHL) including lymphoblastic lymphoma, Burkitt's lymphoma, and large cell lymphoma.

CD22 expression: Patients must have evidence of CD22 positivity by immunohistochemistry and/or FACS analysis

Stage of Disease and Prior Therapy:

- Patients must have measurable or evaluable disease.
- Patients must have relapsed or refractory disease after at least one standard chemotherapy and one salvage regimen.
- In the view of the PI and the primary oncologist, there must be no available alternative curative therapies and patients must either be ineligible for a hematopoietic stem cell transplant (BMT), have refused BMT, or have disease activity that prohibits the time required to identify a suitable stem cell donor.
- Relapse after prior autologous or allogeneic BMT is allowed. In the event of relapse after prior allogeneic BMT, the patient must be at least day +100 post-transplant.
- Patients must have had their last doses of chemotherapy at least 2 weeks (6 weeks for nitrosoureas) and radiation therapy at least 3 weeks prior to the start of study drug.
- Patients must have recovered from the acute toxic effects of all prior therapy before entry.
- Patients should be off colony stimulating factors (e.g., G-CSF, GM-CSF, EPO) for at least one week prior to entry.
- Patients receiving corticosteroids are allowed provided there has been no change in dose for at least 1 week prior to the start of study drug.
- Patients should be off other investigational agents for at least 30 days prior to entry.

Performance status:

- Patients \geq 12 years of age: ECOG score of 0, 1, or 2
- Patients \leq 12 years of age: Lansky scale \geq 50%

- Patients who are unable to walk because of paralysis, but who are up in a wheel chair will be considered ambulatory for the purpose of calculating the performance score.

Hematological function: A patient will not be excluded because of pancytopenia due to disease based on bone marrow analysis. For non-leukemic patients, the absolute neutrophil count (ANC) must be $> 1000/\text{mm}^3$ and the platelet count $> 50,000/\text{mm}^3$.

Hepatic Function: Patients must have adequate liver function defined as total bilirubin within $\leq 2.0 \text{ mg/dl}$ and transaminases $\leq 5\times$ the upper limit of normal.

Renal function: Patients must have an age-adjusted normal serum creatinine OR a creatinine clearance $\geq 60 \text{ mL/min/1.73 m}^2$.

EXCLUSION CRITERIA

- CNS leukemia or lymphoma as manifested by any of the following:
 - CSF WBC $>5/\mu\text{l}$ and confirmation of CSF blasts.
 - Cranial neuropathies deemed secondary to underlying malignancy.
 - Radiologically detected CNS lymphoma.

Note: History of CNS involvement with no current evidence of CNS malignancy is NOT an exclusion.

- Isolated testicular ALL
- Clinically significant unrelated systemic illness (e.g. serious infections or significant organ dysfunction), which in the judgment of the PI would likely compromise the patient's ability to tolerate this therapy or interfere with the study procedures.
- Patients whose serum neutralizes $> 75\%$ of the activity of $1 \mu\text{g/mL}$ of BL22.
- HIV infection.
- Active hepatitis B or C infection as defined by seropositive for hepatitis B (HbSAg) or hepatitis C and elevated liver transaminases.
- Patients currently receiving other investigational agents.
- Lactating or pregnant females.
- High risk of inability to comply with protocol treatment.

PRETREATMENT EVALUATION

- CD22 analysis may be performed on peripheral blood, bone marrow, or existing pathologic material from outside institutions after obtaining telephone consent.
- BL22 antibodies: A sample will be obtained prior to treatment to rule-out pre-existing neutralizing antibodies to BL22.
- **Disease evaluation**
 - Histologic diagnosis will be confirmed by NIH Hematopathology review.
 - Documentation of all measurable disease and evaluable abnormalities is required.

GENERAL TREATMENT PLAN: This is a phase I trial of intravenous BL-22 administered every other day for three doses. Cycles may be repeated every 28 days. Cohorts of 3 to 6 patients will be accrued at each dose level starting at 10 µg/kg days 1, 3 and 5 and increasing to 20 and 25 µg/kg QOD x 3. Patients will be admitted to the inpatient service to receive the study drug for each cycle.

ACCRUAL: *This protocol is now open for accrual.* Expected accrual will be 18 – 24 patients.